

ANSWERING REVIEWERS

March 04, 2015

Dear Editor,
sorry for the delay in submitting the present revision but for a few days I couldn't have access to the main site of WJ Hepatology.

Please find enclosed the edited manuscript in Word format (file name 16034-edited.doc).

Title: MANAGEMENT OF HEPATOCELLULAR CARCINOMA IN THE ELDERLY

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Name of journal: *World Journal of Hepatology*

ESPS Manuscript NO: 16034

The manuscript has been improved according to the suggestions of the reviewers:

1. Format has been updated
2. Revision has been made according to suggestion of the reviewers

a. Reviewer 00052339

#1 HCC is developed from chronic hepatitis or liver cirrhosis. Is the background of liver disease in aged patients with HCC similar to young patients? The surgical resection is very difficult in B or C stage of Child-Pugh, hence the aged patients reported in the reference papers may be good condition such as chronic hepatitis, but not liver cirrhosis. The author can give the data about ratio of liver cirrhosis in the aged patients with HCC. It is possible that the aged patients might be selected because of good or reserved liver function.

We agree with the referee that this point may be relevant in determining the final outcome especially in patients undergoing liver surgery . This point is now addressed in the paper (page 8 line 25-31).

#2 As well as background liver disease, complication such as cardiovascular disease or renal disease should be analyzed in the aged patients because there was no difference OS or DFS in young or aged patients. The aged patients analyzed here may have less complication.

We agree that information on comorbidities in patients undergoing HCC resection are important to better understand the results on outcome in elderly as compared to younger patients, and this point is now further addressed (page 9, line 18-27).

b. Reviewer 00073425

The paper presents the management of hepatocellular carcinoma in the elderly. The issue is very interesting and important for clinical practice. However, the paper should be a meta analysis based on previously performed and published studies. The Authors should describe what criteria they would use to select analyzed studies. In the paper the Authors devoted a separate subsection to a definition and clinical implication of the elderly. In my opinion it is unnecessary for understanding the results. The paper should more extensively present epidemiology of HCC, instead. The Table 1 and the Table 2 do not contain all references cited in the section Resection and Radiofrequency ablation.

This review was not planned to be a meta-analysis since it covers different topics related to the clinical approach to HCC in elderly patients including epidemiology and clinical implications along with outcomes of different treatment procedures applied to these patients. However, a methodologically organized systematic literature research was performed. Criteria employed to select literature are now reported in the paper (page 4, line 26-31 and page 5, line 1-15)

c. Reviewer 00012963

#1 Providing details of the literature search conducted- what were the databases searched, what years did it cover and what search terms were used?

#2 What criteria were used to select papers included in this review?

#3 Consistent referencing and cross-referencing of the papers selected for this review is needed. For example the section titled "HCC outcome in the elderly" refers to "retrospective subanalyses of observational, in-field surveys" Three papers are cited here and it is unclear if this the entirety of available evidence, or whether they were selected based upon some unspecified criteria. Are the conclusions relating to long-term survival drawn from the same papers, or others, not cited?

We agree with the concern and suggestion of the referee and these issues, as for referee 1, are now better specified in the text. (page 4, line 26-31 and page 5, line 1-15).

In the "HCC outcome in elderly" section the authors wanted to specifically address the issue of outcome of HCC in aged patients as a whole rather than the outcome referring to specific type of treatment, being the latter detailed in the following sections. The three selected papers cited in the above mentioned section are the only ones designed to follow HCC patients prospectively. This is the main reason why we decided to selected them.

Conclusion relating to long-term survival in the section "HCC outcome in elderly" were drawn from the same papers cited in the text.

#4 The section headed "Resection" states that "many authors agree that age is not a risk factor for resection". This statement needs referencing. This section is supported by Table 1, which

includes 6 papers, although a total of 15 papers are being referred to in this section. Reasons why they are not included in the Table need stating, to rule out selection bias.

We considered the referee suggestions and reasons why we included papers in table 1 are now specified in the table title. We included in table 1 four additional studies reporting data on survival at 1,3,5 years and data on disease free survival. In addition, number of reference cited in the tables are now specified.

#5 The RFA section. Two retrospective Japanese studies are presented, but only one is cited. Studies 60-62 are not included in Table 2 and the reason for their exclusion needs clarification.

We accepted the suggestion and table 2 has been modified accordingly

#6 The Conclusion states that “any other therapeutic option should be offered to aged patients” needs qualifying (with regards to available functional reserve and general fitness etc).

We agree with the referee and this aspect is now better specified in the text (page 13, line 4)

#7 A caveat regarding the fact that these recommendations emanate as a result of a review of outcomes in carefully selected patients needs to be included

We agree with this suggestion and the text has been modified accordingly (page 13, line 8-9)

#8 The paper is well written, but a careful proofreading is required. Some examples: The abstract: The sentence commencing with “Conversely major resection” needs rephrasing, as does the one starting with “Available data”. Body of the paper: Second sentence needs rephrasing. The Epidemiological considerations section “more frequently mono-pauci focal” needs attention Tables 1 and 2: Is the column titled “survival” refer to overall, or disease-specific survival? The last column is headed DSF- I assume this refers to DFS.

We considered all the suggestions and the text has been modified accordingly (page 2, line 13-14 - page 2, line 6-10 - page 4, line 2-4 - table 1 and table 2

3. Reference and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Hepatology*.

Sincerely yours

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